Evaluation of Mortality and Cancer Incidence among Alachlor Manufacturing Workers

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Alachlor is the active ingredient in a family of preemergence herbicides. We assessed mortality rates from 1968 to 1993 and cancer incidence rates from 1969 to 1993 for manufacturing workers with potential alachlor exposure. For workers judged to have high alachlor exposure, mortality from all causes combined was lower than expected [23 observed, standardized mortality ratio (SMR) = 0.7, 95% CI, 0.4–1.0], cancer mortality was similar to expected (6 observed, SMR = 0.7, 95% CI, 0.3–1.6), and there were no cancer deaths among workers with 5 or more years high exposure and 15 or more years since first exposure (2.3 expected, SMR = 0, 95% CI, 0–1.6). Cancer incidence for workers with high exposure potential was similar to the state rate [18 observed, standardized incidence ratio (SIR) = 1.2, 95% CI, 0.7–2.0], especially for workers exposed for 5 or more years and with at least 15 years since first exposure (4 observed, SIR = 1.0, 95% CI, 0.3–2.7). The most common cancer for these latter workers was colorectal cancer (2 observed, SIR 3.9, 95% CI, 0.5–14.2 among workers). Despite the limitations of this study with respect to small size and exposure estimating, the findings are useful for evaluating potential alachlor-related health risks because past manufacturing exposures greatly exceeded those characteristic of agricultural operations. These findings suggest no appreciable effect of alachlor exposure on worker mortality or cancer incidence rates during the study period. *Key words*: agricultural chemicals, alachlor, cancer incidence, mortality. *Environ Health Perspect* 104:728–733 (1996)

There has been significant interest in recent years in the health experience of agricultural workers. Blair et al. (*1*) recently published a meta-analysis of epidemiologic studies of farmers and concluded that farmers have significantly elevated rates of lip cancer, Hodgkin's disease, melanoma, multiple myeloma, stomach cancer, prostate cancer, and leukemia. From these findings, they inferred a possible role for pesticides (i.e., herbicides or insecticides) and other work-related exposures. A major prospective study has been initiated to evaluate risk factors for cancers and nonmalignant diseases for farmers, their families, and for commercial pesticide applicators (*2*).

Fundamental characteristics of agricultural practice make it difficult to assess potential health effects of specific pesticides. The type, amount, and frequency of pesticide use depends on a number of factors including the crop, the level and severity of pest infestation, weather conditions, recommended usage, time of year, availability, and cost. Preemergent herbicides, for example, are used by farmers and pesticide applicators only in the days or weeks before planting. Such an occupational exposure scenario is different from the chronic exposure scenario typical of manufacturing environments. Another complicating factor is that farmers and pesticide applicators frequently use a large number of different pesticides each year, making it difficult to evaluate a single or predominant exposure scenario.

The primary advantage of studying pesticide users is the large number of subjects available to be studied. However, in light of the complications mentioned above, such studies should be supplemented by research on pesticide manufacturing populations. Although manufacturing populations tend to be relatively small, they frequently have chronic exposure to specific pesticides and have worked under conditions where exposures have been characterized or can be fairly well documented.

We initiated a study of mortality and cancer incidence among workers involved in the manufacture of alachlor [2-chloro-2′,6′-diethyl-*N*-(methoxymethyl)-acetanilide], the active ingredient in a family of preemergent herbicides. Monsanto has manufactured alachlor since March 1968 at a plant in Muscatine, Iowa. Registration and domestic use of alachlor began in the 1969 growing season. Since that time, alachlor has been used widely on corn, soybeans, and other crops.

Numerous experimental studies have been conducted to characterize alachlor metabolism and toxicology. Chronic feeding studies at high doses found increased frequencies of nasal, stomach, and thyroid tumors in laboratory rats (*3,4*). The lowest observed effect levels (LOELs) were 126 mg/kg daily for thyroid cancers and 42 mg/kg daily for thyroid tumors (exposure levels that were overtly toxic to rats) and 15 mg/kg daily for nasal cancers. Experimental evidence suggests that the alachlor-related stomach and thyroid tumors result from nongenotoxic mechanisms at exposures that exceeded tolerable doses (*4,5*). These mechanisms are not operative in rats at lower doses.

Mechanistic research on the rat nasal tumors points to a specific alachlor metabolite (2,6-diethylbenzoquinoneimine) that concentrates in rat nasal tissues (*6*). Enzymatic capabilities of rat nasal cells to produce this putative carcinogenic metabolite exceed the capabilities of human nasal cells by three to four orders of magnitude (*7*). Whole-body autoradiographic studies have shown accumulation of radiolabeled alachlor or its metabolites in nasal tissues of rats, but not in monkeys (*7*). It has been estimated that the nasal tumor LOEL exceeds manufacturing exposures in the early years of production by at least 40-fold and typical current agricultural exposures by 25,000-fold (*8*).

An alachlor chronic feeding study in mice found a statistically significant increase in lung tumors among females in the highest daily exposure group (260 mg/kg) (*5*). Lung tumor incidence for this exposure group, however, was within the range of historical control values. A second chronic study in mice did not show any dose-related increase in lung tumors (*9*).

Metabolic studies in monkeys, used to provide a surrogate model for human metabolism, show that oral and dermal alachlor exposures are metabolized and excreted largely through the urinary tract, with a small portion excreted through the large bowel (*10,11*). Alachlor and fecal and urinary metabolites of alachlor are negative in Ames tests (*12*).

Previous studies of alachlor workers from the Muscatine plant have considered ocular effects, mortality for the period 1968–1990, and cancer incidence for the

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period 1970–1990 (*8,13,14*). The present study updates mortality and cancer incidence analyses through 1993 and provides additional analyses of workplace and environmental exposures not addressed in the previous studies.

Methods

The total Muscatine plant population was enumerated from Social Security Administration (SSA) Quarterly Reports on Earnings (form 941A). Demographic and work history information was abstracted from company employment records. The mortality cohort was restricted to the 1199 workers employed at least 1 year from plant start up as an ammonia facility in 1961 through 31 December 1993.

The cancer incidence cohort was a subset of the mortality cohort, including 1169 workers who lived in Iowa for some time during the period 1969–1993. Thirty employees from the mortality cohort were excluded because they either lived nearby in Illinois or transferred to another Monsanto location before 1969. The criterion of Iowa residence reflects the catchment area for the State Health Registry of Iowa (SHRI), which was the source for identifying cancers in this study. The SHRI is a statewide, population-based cancer registry that has been operating since 1969 and has participated since 1973 in the National Cancer Institute's Surveillance Epidemiology and End Results Program.

Vital status was determined for the mortality cohort until the end of 1993 using a variety of sources, including company payroll, pension and mortality files, SSA (a submission prior to 1987 when SSA stopped doing mortality searches for researchers), the National Death Index, the Iowa state motor vehicle bureau, and a retail credit agency. In addition, direct tracing by mail and phone was conducted as part of the cancer incidence evaluation. As a result of these procedures, 1166 (97.3%) workers were found to be alive, 30 (2.5%) were deceased, and 2 (0.2%) were lost to follow-up. The proportions alive, deceased, and lost to follow-up were similar for the 1036 workers judged to have had alachlor exposure (see Table 1).

Death certificates were obtained for all known decedents. Two nosologists independently coded the underlying cause of death (UCOD) for each decedent according to the eighth revision of the International Classification of Diseases (*15*). The UCOD from each nosologist was compared for each decedent and the single disagreement, which involved the coding of an accidental death into different subcategories, was resolved by mutual agreement.

The incidence study cohort was matched against the SHRI master database to identify workers diagnosed with invasive cancer from 1969 through 1993. Cancer cases were identified based on the correspondence between workers' identifying information (social security numbers, full names, and birth dates) in company files and in SHRI's database. All inexact matches were verified by matching other data in the workers' personnel files and in SHRI's records. Incident cancer cases were coded according to the second edition of the International Classification of Diseases for Oncology (*16*). SHRI was also the source for general population Iowa cancer incidence rates, which were used as a basis of comparison for workers' cancer incidence rates.

The major methodologic issue for conducting a valid cancer incidence analysis was correctly enumerating person-years at risk within SHRI's catchment area. We used a number of data linkage and tracing procedures to address this issue. First, current addresses were obtained from company records for active workers and vested former employees (i.e., workers employed long enough to qualify for retirement benefits). Current Iowa residents who lived in Iowa or moved to Iowa when hired at the Muscatine plant were assumed to have lived in Iowa since their plant hire date. Former vested employees who had a current address outside of Iowa (mainly transferees within Monsanto) were assumed to have been Iowa residents from their start date at the Muscatine plant until their transfer or employment termination date. Present workers with a non-Iowa current address and workers who terminated employment before becoming vested were sent a letter to establish their dates of Iowa residency. We also matched these workers with the Iowa Department of Motor Vehicles, the company mortality database, and databases maintained by a credit search firm to establish possible Iowa residency after employment termination. Finally, we traced workers whose residence histories remained unknown through directory assistance and did a phone survey to identify as many residence histories as possible. As a result of these tracing procedures, residence history was determined for 98.4% of workers with potential alachlor exposure as of 31 December 1993 (Table 1). Follow-up improved with length of potential exposure: we determined residence history for all but 2 of 481 employees who had 5 or more years of alachlor exposure. These 2 employees became lost to follow-up 2 years and 1 month, respectively, before the end of study date.

Another methodologic issue concerns cancer incidence of workers who left the SHRI catchment area and were excluded from the cancer incidence analyses as of the date they left. Workers who remained in Iowa had more than twice as many years of alachlor exposure than workers who left Iowa, so migration is not likely to affect the validity of our results. Cancer risk was also assessed through national mortality analyses.

Exposure Assessment

There was insufficient information on plant conditions to estimate alachlor exposures quantitatively during the study period. Therefore, our exposure estimation was qualitative, based on work history information, judgment of an industrial hygienist, and, to a lesser extent, recent exposure monitoring data (*17*).

The first step in the exposure estimating process was the creation of a department/job title dictionary that included all work locations and job assignments in

Table 1. Distribution of workers by gender, alachlor exposure status, and follow-up status

Group	Men	Women	Total
Mortality cohort			
Total	954	245	1199
Nonwhites (excluded from analysis)	20	6	26
Nonalachlor (excluded from analysis)	93	44	137
Alachlor-exposed	841	195	1036
No. alive	817	191	1008 (97.3%)
No. dead	23	4	27 (2.6%)
No. lost to follow-up	1	0	1 (0.1%)
Incidence cohort			
Total	928	241	1169
Nonwhites (excluded from analysis)	20	6	26
Nonalachlor (excluded from analysis)	77	41	118
Alachlor-exposed	831	194	1025
No. in Iowa through 1993	573	142	715 (69.8%)
No. migrated from Iowa before 1993	228	43	271 (26.4%)
No. unknown migration date from Iowa	12	4	16 (1.6%)
Incident cancers	19	5	24[a]

[a]One worker had two incident cancers.

workers' personnel records. Jobs with similar exposure potential were consolidated by the plant industrial hygienist into occupational exposure categories (OEC). The plant hygienist then assigned each OEC a high, medium, low, or negligible qualitative exposure ranking for alachlor as well as for other specific chemicals. The exposure rankings considered changes in exposure potential over time resulting from changes in plant technology as documented by standard manufacturing process reports, industrial hygiene and safety reports, a 25-year chronology of the plant's history, and interviews with long-term employees.

The qualitative exposure rankings were based primarily on the opportunity for dermal contact with alachlor. Inhalation exposures were judged to be an extremely minor component of total exposure due to alachlor's extremely low vapor pressure (1.6×10^{-5} mm Hg at 25°C). Current and historical airborne measurements relative to alachlor vapor have averaged less than 10 ppb. The more recent granular and water dispersible alachlor formulations create the possibility of airborne exposure via dusts, but even in these operations airborne measurements have averaged much less than 100 parts per billion.

The qualitative exposure rankings did not discriminate between daily and intermittent exposures for workers with different jobs in the same department/location. Thus, for a given department/location, production and maintenance workers had the same exposure ranking. However, production workers, particularly those in formulation and packaging operations, had more frequent potential for (dermal) alachlor exposure than maintenance workers, except perhaps for the initial year(s) of the alachlor process when exposures were more similar for these two groups.

A source of exposure of uncertain magnitude and duration was contamination of the plant drinking water. The contamination was discovered incidentally in June 1975. While developing a method for measuring alachlor concentrations in water, a "control" sample from the plant's drinking water showed an alachlor concentration of 2 mg/l (2 ppm). Plant management immediately notified workers and brought in bottled drinking water to eliminate exposure. Soon thereafter the plant's water supply was switched to other wells at the plant. Subsequent alachlor measurements from the new wells averaged 8 µg/l (8 ppb) through 1980. At that time, installation of a carbon filtration system was completed, which reduced alachlor in the water supply to below the minimum detection level of 0.03 µg/l.

Workers' exposure to alachlor from drinking water would depend on the duration of the water contamination at the plant and the amount of water consumed on a daily basis. Both aspects of exposure were unknown to us. However, if we assume a constant well water concentration of 2 mg/l and that workers drank 1 l of plant water daily, we estimate that exposure from drinking water would equal that in high-exposure jobs.

In certain analyses we classified all workers employed from 1968 to 1975 in the high-exposure category (to allow for the maximum possible period of drinking water contamination), even if their jobs entailed no occupational exposure. We also conducted analyses based on various more restrictive periods of drinking water contamination to assess the potential impact of misclassification based on drinking water exposure.

We conducted analyses based only on occupational exposures. A relatively small number of workers had exposure only via drinking water, and excluding these workers from the analysis of alachlor-exposed workers did not appreciably affect the results.

Epidemiologic Analysis

The epidemiologic measures of effect for the mortality and incidence analyses were the standardized mortality and incidence ratios (SMR, SIR). These measures were expressed as the ratio of observed to expected events and are equivalent to the ratio of disease rates for workers and the general population adjusted for age, gender, and calendar period. The numbers of expected deaths or incident cases were calculated by summing the product of the number of employee person-years, stratified by age, calendar period, and gender, and rates for the corresponding groups in the Iowa general population. The Occupational Cohort Mortality Analysis Program was used to conduct the SMR and SIR analyses (*18*). The 95% CI was calculated as a measure of the statistical variability of the SMR or SIR. Approximate CI calculations were employed when the number of observed deaths exceeded five; Fisher exact CIs were calculated in the other instances (*19*).

Enumeration of person-years for the mortality and cancer incidence analyses began 1 year after first employment, in light of the 1 year employment eligibility criterion for cohort enumeration, or on the date of first alachlor exposure, if later.

For the mortality analysis, person-years were accumulated through the end of study date for employees found to be alive, until date lost to follow-up, or until date of death for deceased employees. For the cancer incidence analysis, person-years were accumulated until the end of the study period for employees who were alive and residing in Iowa at the end of study date, until date of death for employees who died in Iowa during the study period, until date of migration from Iowa, until date of last contact (usually employment termination date) for employees with unknown residence histories, or until cancer diagnosis date for incident cases.

SMRs and SIRs were evaluated for workers by the number of years of alachlor exposure and by time since first exposure. We dichotomized the analyses at 5 or more years of exposure and at 15 or more years since first exposure, which divided expected numbers approximately evenly on each dimension.

We excluded 26 non-whites from the analyses due to their small numbers. There were no incident cancer cases among these workers (0.1 expected) and all were alive as of the end of study date. We also excluded employees who did not work in alachlor departments and who were not employed at the plant during the 1968–1975 and 1976–1980 drinking water contamination periods. The major non-alachlor departments included ammonia production and storage before 1968, and acrylonitrile-butadiene-styrene plastics production after 1975.

Results

Mortality

A total of 1036 workers met the criteria for inclusion in the mortality analysis and had potential alachlor exposure in manufacturing jobs or via drinking water. Mortality from all causes combined for these workers was lower than Iowa rates for both the total cohort (27 observed, SMR = 0.7, 95% CI, 0.4–1.0) and for those with 5 or more years exposure and 15 years since first exposure (4 observed, SMR = 0.4, 95% CI, 0.1–0.9). Mortality from cancer was similar to Iowa rates (Table 2; 8 observed, SMR = 0.9, 95% CI, 0.4–1.7), and there were slight to moderate deficits of cancer mortality for workers with 5 or more years of exposure (3 observed, SMR = 0.6, 95% CI, 0.1–1.8) and 15 or more years since first exposure (1 observed, SMR = 0.2, 95% CI, 0–1.1). Results were similar for workers with high alachlor exposure (Table 2).

SMRs for specific cancers, heart disease, and accidents are given in Table 3 for workers with high alachlor exposure. There were no deaths due to stomach, thyroid, and nasal cancer (the three tumors observed in the chronic feeding studies of

laboratory rats) versus the small expected values. The six observed cancer deaths were distributed among six different cancer sites, and there were no noteworthy findings for specific cancers. Ischemic heart disease mortality was somewhat less than expected. Mortality from accidents was similar to Iowa rates for the total highly exposed subgroup and for those with 5 or more years of exposure and 15 or more years since first exposure.

Cancer Incidence

A total of 1025 white males and females met the criteria for the cancer incidence analyses and were estimated to have potential exposure to alachlor either in their jobs or via drinking water. Linkage with SHRI identified 37 cancers during the study period, 13 of which were *in situ* carcinomas, mostly cervical (n = 9) and skin (n = 2), and 24 were invasive cancers in 23 individuals. *In situ* cancers were not included in our analyses because SHRI incidence rates are routinely based on invasive cancers (with the exception of bladder cancer) and because population-based ascertainment of *in situ* cancers is questionable, especially for the cervix and skin melanoma.

Over the 1969–1993 study period, cancer incidence was slightly higher for alachlor workers than for the Iowa general population (24 observed, SIR = 1.4, 95% CI, 0.9–2.1; Table 4). SIRs were similarly elevated for workers during active employment (14 observed, 11.1 expected, SIR = 1.3, 95% CI, 0.7–2.1) and after employment termination (10 observed, 6.0 expected, SIR = 1.7, 95% CI, 0.8–3.0), suggesting that employment status was not a factor affecting cancer ascertainment. The cancer SIR varied by duration of exposure and time since first exposure (Table 4). The SIR was elevated for workers with less than 5 years of employment and less than 15 years since first exposure (10 observed, SIR = 1.9, 95% CI, 0.9-3.6). The 10 cancers were varied and included 1 salivary gland, 1 rectum, 1 female breast, 1 cervix, 1 uterus, 1 testis, 1 melanoma, 2 Hodgkin's disease, and 1 chronic myeloid leukemia (CML). Workers with 5 or more years of exposure (13 observed, SIR = 1.3, 95% CI, 0.7–2.2) and workers with 15 or more years since first exposure (9 observed, SIR = 1.2, 95% CI, 0.6–2.3) had cancer incidence similar to expected values. During the 1991–1993 update period, there were 6 observed and 5.3 expected cancers (SIR = 1.1, 95% CI, 0.4–2.5).

Of the 1025 alachlor workers, 701 (68%) were classified as having the potential for high exposures. These high exposures included occupational exposures and

Table 2. Standardized mortality ratios (SMRs) for all cancer for employees with potential alachlor exposure (workplace and drinking water)

Duration of exposure/ time since first exposure	No. of workers[a]	Person-years[a]	O/E deaths[b]	SMR	95% CI
All alachlor exposed workers					
<5 years/<15 years	1,036	8,774	4/2.6	1.5	0.4–3.9
<5 years/15+ years	336	1,687	1/1.8	0.6	0–3.1
5+ years/<15 years	485	4,452	3/1.9	1.6	0.3–4.7
5+ years/15+ years	434	2,488	0/3.0	0	0–1.3
Total	1,036	17,400	8/9.3	0.9	0.4–1.7
Workers with high alachlor exposure					
<5 years/<15 years	708	8,249	3/2.7	1.1	0.2–3.3
<5 years/15+ years	520	2,565	1/2.3	0.4	0–2.4
5+ years/< 15 years	159	1,553	2/0.8	2.5	0.3–9.0
5+ years/15+ years	160	1,445	0/2.3	0	0–1.6
Total	708	13,812	6/8.1	0.7	0.3–1.6

[a]Number of workers not mutually exclusive across groups, though person-years are.
[b]Observed number of deaths/expected number of deaths.

Table 3. Standardized mortality ratios (SMRs) for various causes of death for employees with potential high alachlor exposure (workplace and drinking water)[a]

	Total[b]			5+ years exposure; 15+ years since first exposure[c]		
Cause of death (ICD 8)	O/E[d]	SMR	95% CI	O/E	SMR	95% CI
All causes (0–999)	23/34.4	0.7	0.4–1.0	4/7.6	0.5	0.1–1.4
All cancers (140–209)	6/8.1	0.7	0.3–1.6	0/2.3	0	0–1.6
Stomach cancer (151)	0/0.2	—	—	0/0.1	—	—
Thyroid cancer (193)	0/0.04	—	—	0/0.01	—	—
Lung cancer (162)	1/2.3	0.4	0–2.4	0/0.8	—	—
Colorectal cancer (153,154)	0/0.8	—	—	0/0.3	—	—
Breast cancer (174)	0/0.3	—	—	0/0.1	—	—
Prostate cancer (185)	0/0.2	—	—	0/0.1	—	—
Kidney cancer (189)	0/0.2	—	—	0/0.1	—	—
Leukemia (204–207)	1/0.4	—	—	0/0.1	—	—
Brain cancer (191, 192)	0/0.6	—	—	0/0.1	—	—
Hodgkin's disease (201)	0/0.2	—	—	0/0.02	—	—
Melanoma (172)	0/0.3	—	—	0/0.1	—	—
Ischemic heart disease (410–3)	4/7.1	0.6	0.2–1.4	1/2.1	0.5	0–2.6
Accidents (800–949)	8/7.2	1.1	0.5–2.2	0/0.6	—	—

[a]SIRs and 95% CIs were not calculated unless there were at least two observed or expected deaths.
[b]708 workers, 13,811 person years.
[c]160 workers, 1,652 person years.
[d]Observed number of cases/expected number of cases.

Table 4. Standardized incidence ratios (SIRs) for all cancer for employees with potential alachlor exposure (workplace and drinking water)

Duration of exposure/ time since first exposure	No. of workers[a]	Person-years[a]	O/E[b]	SIR	95% CI
All alachlor-exposed workers					
<5 years/<15 years	1,024[c]	6,585	10/5.2	1.9	0.9–3.6
<5 years/15+ years	193	871	1/1.9	0.5	0–3.0
5+ years/<15 years	481	4,122	5/4.6	1.1	0.3–2.5
5+ years/15+ years	383	2,076	8/5.5	1.5	0.6–2.9
Total	1,025	13,654	24/17.1	1.4	0.9–2.1
Workers with high alachlor exposure					
<5 years/<15 years	700[d]	6,787	6/5.8	1.0	0.4–2.3
<5 years/15+ years	387	1,676	5/3.3	1.5	0.5–3.5
5+ years/<15 years	159	1,455	3/1.7	1.8	0.4–5.3
5+ years/15+ years	138	1,179	4/3.8	1.0	0.3–2.7
Total	701	11,097	18/14.6	1.2	0.7–2.0

[a]No. of workers not mutually exclusive across groups, though person-years are.
[b]Observed number of cases/expected number of cases.
[c]One worker moved into the Iowa study area after achieving either 5 years of exposure or 15 years since first exposure.
[d]Two workers moved into the Iowa study area after achieving either 5 years of high exposure or 15 years since first high exposure.

presumed drinking water exposures during the 1968–1975 period. Cancer incidence was fairly similar for these workers and the Iowa population (18 observed, SIR = 1.2, 95% CI, 0.7–2.0) (Table 4). Analyses that considered only 1974–1975 as the period of drinking water exposure gave similar results (17 observed, SIR = 1.3, 95% CI, 0.8–2.1). Workers exposed 5 or more years with at least 15 years since first exposure had 4 observed and 3.8 expected cancers (SIR = 1.0, 95% CI, 0.3–2.7).

Results for specific cancers for workers with high exposure showed no observed cases or 1 case for most sites and elevated SIRs for colorectal cancer, chronic myeloid leukemia (CML), Hodgkin's disease, and melanoma based on 3, 2, 2, and 2 cases, respectively (Table 5). One of the CML cases was diagnosed soon after first employment at the plant, which, given the course of CML, indicates etiologic factors before employment at the plant. Among workers with 5 or more years of exposure, there were no cases of CML or Hodgkin's disease, 1 case of melanoma (0.2 expected), and 2 colorectal cancer cases (SIR 3.9, 95% CI, 0.5–14.2). The results were similar for all alachlor-exposed workers.

We did a further analysis of cancer incidence focusing on 429 alachlor production workers. Our definition of production workers allowed for a maximum of 90 days in maintenance jobs. Many of these workers were employed in formulation and packaging operations, where there was potential for high dermal exposure on a daily basis during the early years of production. Among workers with less than 5 years exposure, there were 7 observed versus 4.5 expected cancers (SIR = 1.6, 95% CI, 0.6–3.2), while for workers with 5 or more years exposure, there were 2 observed versus 2.2 expected cancers (SIR = 0.9, 95% CI, 0.1–3.3). Overall, there were no observed cases of colorectal cancer versus 0.6 expected, 1 case of CML versus 0.1 expected, and no cases of malignant melanoma versus 0.6 expected.

Table 5. Standardized incidence ratios (SIRs) for various cancers for employees with potential high alachlor exposure (work place and drinking water)[a]

	Total[b]			5+ years exposure; 15+ years since first exposure[c]		
Cancer site/type (ICD-0–2 codes)	O/E[d]	SIR	95% CI	O/E	SIR	95% CI
All cancers	18/14.6	1.2	0.7–1.9	4/3.8	1.0	0.3–2.7
Lung (C339–49)	1/1.9	—	—	1/0.8	—	—
Colorectal (C180–9,C260,C199,C209,C210–8)	3/1.6	1.9	0.4–5.6	2/0.6	3.9	0.5–14.2
Breast (C500–9)	1/1.2	—	—	0/0.2	—	—
Prostate (C619)	0/0.7	—	—	0/0.3	—	—
Kidney (C649)	0/0.5	—	—	0/0.2	—	—
Bladder (C670–679)	0/0.7	—	—	0/0.2	—	—
Hodgkin's disease (M9650–9667)	1/0.5	—	—	0/0.04	—	—
Non-Hodgkin's lymphoma (M9590–5,M9670–9714)	2/0.8	2.4	0.3–8.8	0/0.2	—	—
Chronic myeloid leukemia (M9863,M9868)	2/0.1	18.6	2.3–67.2	0/0.02	—	—
Other leukemias (M9800–9941, excluding M9863,9868)	0/0.4	—	—	0/0.1	—	—
Testes (C620–29)	1/0.8	—	—	0/0.1	—	—
Melanoma (C440–9, M8720–90 only)	2/1.1	1.9	0.2–6.7	1/0.2	—	—

[a]SIRs and 95% CIs were not calculated unless there were at least two observed or expected cases.
[b]701 workers, 11,097 person years.
[c]138 workers, 1,179 person years.
[d]Observed number of cases/expected number of cases.

Discussion

The purpose of this study was to monitor patterns of cancer mortality and incidence for alachlor workers, especially for cancer sites seen in chronic feeding studies of rats, and to follow-up on the slight colorectal cancer excess seen in the previous incidence study (*14*). We did not see a relationship between cancer incidence and years of alachlor exposure or time since first exposure, and there were no cancers of the thyroid, stomach, or nose and nasal sinuses among exposed workers. The numbers of observed and expected cases were small for most cancer sites, which makes the SMRs and SIRs imprecise and precludes informative exposure–response analyses for individual cancer sites.

There were no new colorectal cancer cases during the update period versus 0.6 expected, lessening the observed/expected ratio previously reported (*14*). This observation, in conjunction with the lack of any cases among workers in formulation and packaging and the minor involvement of the large bowel in alachlor metabolism and excretion, tends to support a noncausal interpretation of the colorectal cancer findings for this cohort. Further follow-up of these workers will be important to monitor incidence from colorectal and other cancers.

The major limitation of this study is the small numbers of incident cancers and cancer deaths. The cohort is still relatively young (74% of person years under observation were less than 40 years of age), and the follow-up period is relatively short. In terms of power, the study had more than 80% power to detect a relative risk of 2.0 for all cancers, but the power for major individual cancer sites would exceed 80% only for relative risks of 5 or higher (*20*).

A second limitation is the possibility of exposure misclassification due to the difficulty in estimating dermal occupational exposures, for which there is no accepted methodology even today, and exposures from plant drinking water. Exposure estimation, however, is more straightforward for these workers than for agricultural populations because the plant manufacturing history is well documented, there is a long standing industrial hygiene program, and work history records documenting departmental assignments and workers' jobs were fairly complete.

Despite the limitations of this study, the findings are useful for assessing potential alachlor-related health risks. The exposure circumstances for this manufacturing cohort are unique among alachlor-exposed workers, the vast majority of whom are involved in agricultural applications for a few days or weeks each year. It has been estimated that the relatively high daily exposures characteristic of early manufacturing operations exceed exposures in agriculture by several orders of magnitude (*8*). If this is true, then this study has exposure weighted years of observation equivalent to an extremely large study of agricultural workers. Periodic follow-ups of this cohort, in conjunction with an on-going, large, prospective study of farmers and applicators (*2*), should provide the most comprehensive assessment possible of potential health risks for workers with various levels of alachlor exposure. At present, however, the available data from manufacturing workers do not indicate an appreciable hazard during the study period related to alachlor exposure.

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